

Navigating Market Authorisation in the UK for the pharmaceutical industry

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Introduction

1. 'Marketing Authorisation' must be obtained in respect of any medicinal product that is to be sold, supplied or offered for sale or supply in the UK. This article looks at the different types of authorisation available, including when they might be appropriate for use in respect of the UK only before considering the process adopted in the UK for approving medicines into the market. It is designed to be a beginner's guide to bringing new products to market in the UK as opposed to a full explanation of each step; ultimately how the application itself is made will depend on the product itself and the research behind it. If upon reading this article you gain an understanding of how to begin the Market Authorisation process, then this article has served its purpose.
2. NB: This article examines the Market Authorisation process only in relation to medicinal products seeking to enter the UK market. It does not deal with the Parallel Import Licence scheme, applying for a Traditional Herbal Registration, or for licensing homeopathic medicines for which there are separate processes.

The Medicines and Healthcare product Regulatory Authority

3. Any manufacturers looking to bring a medicinal product to market in the UK will become very familiar with the Medicines and Healthcare Products Regulatory Authority ("the MHRA").
4. The MHRA is an executive agency sponsored by the Department of Health and Social Care that regulates medicines, medical devices and blood components in the UK.
5. It has six primary responsibilities:

- a. Ensuring that medicines, medical devices and blood components for transfusion meet applicable standards of safety, quality and efficacy;
 - b. Ensuring that the supply chain for medicines, medical devices and blood components is safe and secure;
 - c. Promoting international standardisation and harmonisation to assure the effectiveness and safety of biological medicines;
 - d. Helping to educate the public and healthcare professionals about the risks and benefits of medicines, medical devices and blood components, leading to safer and more effective use;
 - e. Supporting innovation and research and development that's beneficial to public health; and
 - f. Influencing UK, EU and international regulatory frameworks so that they're risk-proportionate and effective at protecting public health.
6. Part of the MHRA's role is administering and validating applications for Marketing Authorisation in the UK. Therefore for any companies looking to introduce new medicinal products into the UK market, liaising with the MHRA to secure Market Authorisation is a crucial step.

Routes to Marketing Authorisation and which route to use

7. There are four routes to getting Marketing Authorisation within the UK:
- a. The National Procedure – this route is used where manufacturers wish to market their products in the UK only and the product is not within the mandatory requirements of the EU Centralised Procedure;
 - b. The Mutual Recognition Procedure – this route is used where manufacturers wish to market their product within the UK (amongst other EU member states) and where the product has already received Market Authorisation in another member state;
 - c. The Decentralised Procedure – this route is used where manufacturers wish to market their products for the first time in the UK and other member states.

- d. The European Centralised Procedure – this is an obligatory process for some particular types of medicines in the UK (see below).

National Procedure

8. The first thing applicants need to be aware of is that the National Procedure takes around 210 days (i.e. around 7 months), excluding the time taken to provide further clarifying information when sought by the MHRA.
9. In respect of the process it is fairly straightforward:
 - a. Obtain a five-digit company number (unless already in possession of one).
 - b. Obtain a product licence (PL) number from the MHRA Portal or by emailing Area0-PLNumberAllocation@mhra.gsi.gov.uk before submitting an application. Advice can be sought pre-application by contacting: 020 3080 7400 or RIS.NA@mhra.gsi.gov.uk.
 - c. Use the electronic Common Technical Document (eCTD) for your submission.
10. It is the National Procedure upon which the remainder of this article shall focus once the other three options have been outlined.

Mutual recognition procedure

11. The mutual recognition procedure is used when both of the following conditions apply:
 - a. A medicinal product has already received Market Authorisation in one or more EU member states but the holder wishes to market that product in other EU countries; and
 - b. The medicinal product does not fall within the mandatory scope of the centralised procedure (see below).
12. Identical applications for Market Authorisation must be submitted to one or more member states using the member state's own Market Authorisation processes. The member state that initially granted Market Authorisation leads the application whilst the other member states await a decision from the lead member state before undertaking their own considerations.

13. Where your product has obtained Market Authorisation in the UK and you wish to begin the Mutual Recognition Procedure, you should email MR-DCprocedures@mhra.gsi.gov.uk with the name of the product and the PL number.

Decentralised procedure

14. The decentralised procedure is similar to the mutual recognition procedure, however, it is used when a medicinal product has yet to receive Market Authorisation in a member state at the time of application.
15. To begin the decentralised procedure, applicants first select a lead member state and submit identical applications to the lead member state and the relevant authorities of the other member states in which they wish to obtain Market Authorisation. Once the lead member state has conducted its evaluation, a draft assessment report, summary of product characteristics, labelling and package leaflet are approved.
16. Thereafter the mutual recognition process is used.
17. To begin an application with the UK as the lead member state you are required to book a submission date using the MHRA's decentralised procedure request form available on its website.

Centralised procedure

18. The centralised procedure allows applicants to obtain Market Authorisation that is valid throughout the EU as well as Iceland, Lichtenstein and Norway.
19. The procedure is mandatory for certain types of medicinal products and is available as an option for certain others. Mandatory products include:
 - a. Medicinal products developed by means of specified biotechnological processes;
 - b. Medicinal products for human use containing a new active substance which, as at 20 May 2004 was not authorised in the European Community and for which the therapeutic indication is the treatment of:
 - i. AIDS;
 - ii. cancer;
 - iii. neurodegenerative disorder;

- iv. diabetes;
 - v. auto-immune disease and other immune dysfunctions; or
 - vi. viral diseases.
- c. Advanced therapy medicines.
- d. Orphan medicines.
20. The centralised procedure is available as an option for:
- a. Any other products containing new active substances not authorised in the EU before 20 May 2004;
 - b. Products which constitute a significant therapeutic, scientific or technical innovation; or
 - c. Where EU authorisation is in the interests of patients at Community level.

National Procedure - What type of application should I make?

21. There are two types of application that can be made under the National Procedure to the MHRA:
- a. A full (or standalone) application; or
 - b. An abridged application.

Full application

22. A full application must be used where the product for which Market Authorisation is sought contains a new active substance.
23. The submission must contain the following information/documentation:
- a. The name or corporate name and permanent address of the applicant and, where applicable, of the manufacturer;
 - b. The name of the medicinal product;
 - c. Qualitative and quantitative particulars of all the constituents of the medicinal product, including the reference to its international non-proprietary name

- recommended by the World Health Organisation, where one exists, or a reference to the relevant chemical name;
- d. An evaluation of the potential environmental risks posed by the medicinal product;
 - e. A description of the manufacturing method;
 - f. Therapeutic indications, contra-indications and adverse reactions;
 - g. Posology, pharmaceutical form, method and route of administration and expected shelf life;
 - h. Reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of potential risks presented by the medicinal product for the environment;
 - i. A description of the control methods employed by the manufacturer;
 - j. A written confirmation that the manufacturer of the medicinal product has verified compliance with good manufacturing practises of active substances by conducting audits. Such confirmation should contain a reference to the date of the audit and a declaration that the outcome of the audit confirms that the manufacturing complies with the principles and guidelines of good manufacturing practice;
 - k. The results of:
 - i. pharmaceutical tests (physico-chemical, biological or microbiological) tests;
 - ii. pre-clinical tests (toxicological and pharmacological) tests; and
 - iii. clinical trials.
 - l. A summary of the applicant's pharmacovigilance system which shall include the following elements:
 - i. proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance;
 - ii. the Member States in which the qualified person resides and carries out his/her tasks;
 - iii. the contact details of the qualified person;

- iv. a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil their legal tasks and responsibilities;
 - v. a reference to the location where the pharmacovigilance system master file for the medicinal product is kept.
- m. The risk management plan describing the risk management system which the applicant will introduce for the medicinal product concerned, together with a summary thereof;
- n. A statement to the effect that clinical trials carried out outside the European Union met the EU ethical requirements for clinical trials as outlined within Directive 2001/20/EC;
- o. A summary of the product characteristics, a mock-up of the outer packaging, and of the immediate packaging of the medicinal product, together with a package leaflet;
- p. Proof that the manufacturer is authorised in his own country to produce medicinal products;
- q. Copies of the following:
 - i. any authorisation, obtained in another member state or in a third country, to place the medicinal product on the market;
 - ii. a summary of the safety data including the data contained in the periodic safety update reports, where available, and suspected adverse reactions reports;
 - iii. a list of those member states in which an application for authorisation is under examination;
 - iv. a summary of the product characteristics and package leaflet submitted to another member state;
 - v. details of any decision to refuse authorisation, whether in the Union or in a third country, and the reasons for such a decision.
- r. A copy of any designation of the medicinal product as an orphan medicinal accompanied by a copy of the relevant Agency opinion.

Abridged application

24. Where the product for which Market Authorisation is sought contains existing active ingredients then an abridged application can be submitted allowing applicants to rely on pre existing clinical data.
25. There are five types of abridged applications:
- a. Generic applications – an applicant is not required to provide the results of pre-clinical tests and of clinical trials if it can be demonstrated that the medicinal product is a generic medicinal product which is or has been authorised for at least eight years in a Member State or in the Community;
 - b. Hybrid or similar biological applications – pre clinical test and clinical trial results will be required where:
 - i. The strict definition of a general medicinal product is not met
 - ii. Where bioavailability studies cannot be used to demonstrate bioequivalence;
 - iii. Where there are changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration of the generic product compared to the reference product.
 - c. Well-established use applications - If active substances of the medicinal product have been in well-established medicinal use within the Community for at least ten years, with recognised efficacy and an acceptable level of safety test and trial results can be replaced by appropriate scientific literature.
 - d. Fixed combination applications – where the medicinal product contains active substances used in the composition of authorised medicinal products but not in combination for therapeutic purpose then the results of new pre-clinical tests or new clinical trials relating to that combination must be provided but it shall not be necessary to provide scientific references relating to each individual active substance.
 - e. Informed consent applications.

Conditions of authorisation

26. Before granting Market Authorisation the MHRA must be satisfied that:
- a. The applicant has established the therapeutic efficacy of the medicine;
 - b. The positive therapeutic effects of the medicine outweigh the risks to health of patients or of the public associated with the medicine;
 - c. The application and the accompanying materials are in accordance with *regulations 49 to 55* of the Human Medicines Regulations; and
 - d. The medicine's qualitative and quantitative composition is as described in the application and the accompanying material.

Grant of Market Authorisation

27. Where an application for Market Authorisation is approved it is valid for five years. Following successful renewal, it is indefinite unless concerns about the products safety subsequently arise.
28. However, of importance is that once Market Authorisation has been granted, products must be placed onto the UK market within three years of the date of authorisation otherwise Market Authorisation lapses and must be re-sought.
29. Similar, if the product is withdrawn from the market for three years, Market Authorisation is withdrawn.

Negative outcome

30. Prior to receiving a negative outcome, an applicant will receive a provision opinion from the MHRA that Market Authorisation cannot be granted. The applicant then has 28 days to request to make written or oral representations regarding the same. Written representations or supporting documents for oral representations must normally be supplied to the committee within six months of the request being made.

Conclusion

31. It is hoped that the reader will now have a basic understanding of the process to take new medical products from testing to placement in the UK market.
32. For a discussion on any topics arising from this article then please do not hesitate to contact me on matthew.wyard@3pb.co.uk / 0117 928 1520.

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